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Biomedicine and Molecular Biology

Design of a tool to force the controlled suicide in human cells

When cells accumulate excessive errors in the proteins they produce, apoptosis is activated, i.e. their suicide. However, before that they try to solve the problem with a range of salvation responses. The stress response mechanisms available to cells are only roughly known. Scientists at the Institute for Research in Biomedicine (IRB Barcelona) have designed a new tool to study in detail the means of salvation and cell suicide. The description of the new method has been published in *Nucleic Acid Research*.

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Scientists will use the new tool to investigate fully the rescue mechanisms that cells have to fix genome errors and to identify targets of therapeutic interest. "We have developed a strategy to create problems for the cell in a controlled manner, so that it gradually turns the various repair systems until opting for auto-elimination [apoptosis]," explains the author of the article, Lluís Ribas de Pouplana, ICREA researcher and head of the Genetic Translation Laboratory of the IRB Barcelona.

The common techniques includes exposing the cell to drugs or compounds that affect protein production, and therefore creating instability. Renaud Geslain, researcher of the Ribas group and first author of the article, "he had a great idea to reproduce the same effect internally, without the help of foreign compounds in the cell," details Ribas. Geslain manipulated a component of the production system of cell proteins that forces it to produce defective proteins.

One of the pieces involved in the production of proteins is the transfer RNA (tRNA), whose function is to transport the protein synthesis machinery, the necessary and precise amino acids for each protein under construction. Geslain designed new tRNAs, very similar to the natural ones, but which puts the wrong amino acids to the proteins under construction. Because the researchers know which modification they introduced in the production of proteins, they can measure the different reactions of the cell according to the produced error. There are more serious mutations that make the cell activate the suicide within 48 hours, whilst changes that are lighter, allow the cell to survive up to 5 days.

In the lab they have already begun to obtain results using this new tool. The analysis indicate that part of the answer to poor protein accumulation passes through the production of various micro-RNAs, small molecules that regulate the expression of genes whose function is still unknown.

But also, Ribas continues, "the biological problem that we create to the cell, the accumulation of defective proteins, is directly linked to neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington, that are caused by adding proteins that are badly folded and which cause neuronal death". The new tool developed at the IRB Barcelona will identify new components of the response mechanisms for this problem that later could become targets for intervention in these or other diseases.